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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K — A2

(11) International Publication Number: WO 99/55286

(43) International Publication Date: 4 November 1999 (04.11.99)

(21) International Application Number: PCT/US99/09547

(22) International Filing Date: 30 April 1999 (30.04.99)

(30) Priority Data:
09/070,940 30 April 1998 (30.04.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 09/070,940 (CON)
Filed on 30 April 1998 (30.04.98)

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: DRUG-CONTAINING TRANSDERMAL PATCHES, PLASTISOLS AND ADHESIVES

(57) Abstract

Drug delivery polymer systems include hydrophobic polymer and a drug that has an aromatic ring. The system comprises, on a carrier (10), a layer (12) comprising the pressure sensitive adhesive having solids in which a drug is substantially soluble, a non-adhesive polymeric resin distributed uniformly in non-particulate manner through the adhesive, in which the drug is substantially soluble, and drug. Another delivery system comprises a non-adhesive layer (14) of polymeric resin in which a drug component is substantially soluble and an adjoining adhesive band (18) arranged to hold the non-adhesive layer against the skin. In both, the drug comprises at least 10 % by weight of the drug-containing layer, preferably in excess of 20 %, or 30 % or 40 % by weight. It is discovered that concentrations in excess of 50 % and 60 % can be achieved in effective formulations. The layer can be thin so that, despite high concentration no more than about 30mg drug per inch square is present, preferably less than 20mg or 10 mg per inch square. In embodiments that achieve a high concentration, the drug component comprises at least two drugs, one of which is soluble in the other, a solution of the drugs in the quantities present in the layer having a melting temperature below room temperature, and lower than the melting temperature of either drug alone. A congealed plastisol layer comprising tetracaine, lidocaine and polyvinyl chloride, is particularly effective for topical anesthetic. Methods of manufacture and preparatory compositions have now been disclosed.

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DRUG-CONTAINING TRANSDERMAL

PATCHES, PLASTISOLS AND ADHESIVES

U.S. Patent No. 5,279,594 was the first disclosure of a series that represents an important breakthrough in drug delivery. U.S. 5,279,594 showed that high, effective concentrations of drugs such as lidocaine base could be incorporated in wall-forming polymers such as polyvinyl chloride (PVC), the drug-containing plastic serving as an effective delivery vehicle for the drug.

Use of lidocaine, an acetamide, and dibucaine, an amide were illustrated and anesthetizing products were described, including urethral, endotracheal and naso-gastric tubes and elastic films having surfaces formed of the plastic material.

Methods for making these products shown in U.S. 5,279,594 included process solution; heating and pressing; and gas diffusion.

Related U.S. Patent, No. 5,417,571, disclosed that high concentrations of such drugs in base form in plastic such as PVC perform the function of a plasticizer for the plastic objects. Products produced by extrusion and coextrusion techniques, incorporation of the plastic in implants, and use of drug in the plastic for antiarrythmia medication were described.

World Patent application, published as WO95/08305 discloses further use of drugs carried in this manner for antiarrythmia and antiseizure treatment.

The disclosure of WO 98/39042 showed that other drugs having similar chemical structure enter solution or

otherwise are compatible in substantial concentrations and can be incorporated in plastic in form enabling it to be administrable by skin patch, for controlled release.

Broadly, the principles apply to drugs having at least one aromatic ring (substituted or unsubstituted benzene ring) that includes at least one free amide or amine hydrogen in its structure. In particular, drugs having at least one aromatic ring (e.g., at least one substituted or unsubstituted benzene ring), and melting point in the range of the processing temperature of thermoplastic or other heat processable resins, with the drug in base form (e.g., includes at least one free amide or amine hydrogen in its structure), can be dissolved or otherwise incorporated in effective concentrations in heat processable resin, typically at elevated temperature. In many instances, the concentrations of the drug can be very high, e.g. in excess of 10% by weight, in many cases preferably in excess of 20% by weight, and most preferably in excess of 30% or 40% by weight. For many conventional low or medium molecular weight resins having processing temperatures between about 250°F and 350°F, numerous of the drugs have been found to be soluble or otherwise capable of incorporation at useful levels. For high molecular weight resins, with processing temperatures up to about 450°F, additional drugs may be dissolved or incorporated at useful levels.

In the cooled form, the solution of resin and drug may behave as they do in conventional plastized PVC, forming, in essence, a solid gel, which, in many useful cases, has a desirable rubbery consistency. In other cases, a network of the drug is distributed through the cooled reservoir resin, in molecular, crystalline or amorphous form, that can be utilized via migration

through the resin or by access pathways provided in the reservoir.

In a preferred form, it was shown that drugs employed according to the invention have the form:

$$Bz - Z - (CH_2)_n - NR^1 R^2$$

where:

Bz is a substituted or unsubstituted benzene ring;
Z is an ester or amide linkage;
and each R^1 and R^2, individually, is Hydrogen or an alkyl group, or together form a 5 or a 6 member ring with the Nitrogen, and n is an integer.

For a desired drug, the resin system is selected to be compatible with the drug such that, at processing conditions and conditions of use, no adverse effects or reactions occur that deprive the drug of its efficacy, or the degree of mobility of the drug desired. For instance, when using thermal processing techniques, the ingredients are selected to withstand the temperatures of processing and the shear forces that are involved in the mixing, milling, or extruding that is involved and to be biocompatible when exposed to the patient.

It was observed, specifically that numerous drugs are highly soluble in polyvinyl chloride, chlorinated polyethylene and ethylene propylene, as well as in methyl methacrylate and other acrylics. It has been observed that these drugs have at least one benzene ring, are of base (e.g., free amine or amide) form. They have a lower melting point than the hydrochloric salt form of the drug, that makes them practically processable with thermoplastic resins, e.g. at temperatures in the range of about 250°F to 350°F, and up to 450°F for high molecular weight resins.

Broadly speaking, it has been explained that the principles are indicated to be applicable to resins or polymers in which plasticizers can be incorporated or in which phthalates, glycolates or citrate esters are soluble, or in which plasticizers or other additives with at least one aromatic ring can be incorporated, and that the solubility or ability to be incorporated in resins of such drugs of such molecular structure as described, in a general way, is predictable from the behavior in resins of comparable plasticizers such as phthalate, glycolate, and citrate esters which are also characterized by an aromatic ring. For the class of drugs having an aromatic ring, and especially a single aromatic ring, it was proposed that such drugs will have solubilities or the ability to be incorporated in the range of plastics in which plasticizers of similar molecular structure are soluble or can be incorporated. Phthalate esters are soluble, or can be incorporated e.g. in polymers and copolymers of polyvinylchloride, chlorinated polyethylene, cellulose nitrate, ethyl cellulose, cellulose acetate, polystyrene, polyvinyl butyryl, acrylic resins, alkyl alkylacrylates, acrylonitrile rubbers, and chlorinated rubbers such as neoprene. Drugs having a single benzene ring and structure similar to the plasticizers are likewise soluble or incorporatable in the range of resins, as a step in the preparation of a drug delivery composition.

As has thus been indicated, the original discoveries, which arose in respect of topical anesthetics, have led to the realization that the system has generality beyond drugs that are known to have anesthetic characteristics. Thus, from the similarity of chemical structure and known characteristics of drugs, plasticizers and resins, it is realized that a wide range of drugs having sufficient unsaturated moieties, aromatic

or heteroaromatic moieties, or similar structure can be delivered employing the present invention.

Further aspects described in WO 98/39042 included the following features. The drug has local anesthetic properties (whether or not it is generally used as a local anesthetic); the drug is an antiarrhythmic or antiseizure drug having local anesthetic properties; the antiarrhythmic drug is propafenone or lidocaine; the drug is a local or topical anesthetic medication; the drug is an adrenergic blocking drug such as atenol; the drug is a sympathomimetic drug such as pseudoephedrine, terbutaline or phenylpropanolamine; the drug is an analgesic or antipyretic such as acetaminophen, phenacetin or ibuprofen; the drug is a stimulant of the nervous system, e.g. a psychostimulant such as methylphenidate.

It was explained that structurally related drugs may be incorporated in a number of biocompatible polymers or copolymers without preventing the drug from having efficacy. Examples include resins selected from polyvinyl chloride, other polymerized vinyl halides, chlorinated polyethylene, other halogenated polyolefins, cellulosic resins such as cellulose nitrate, ethyl cellulose, cellulose acetate, polystyrene, polyvinyl butyryl, alkyl alkylacrylate resins (e.g., methyl methacrylate, ethyl methacrylate), or alkyl acrylates, acrylonitrile rubbers, and halogenated rubbers (e.g., chlorinated neoprene), polyesters such as polyethylene terepthalate, polyamides such as nylon and polyformaldehyde.

WO 98/39042 also disclosed the applicability of general knowledge of the plastics industry as to compatibility of particular plasticizers, solvents, and other additives with known structural and film forming

plastic systems. The molecular structure of the base form of a drug having a benzene ring, that is desired to be delivered, is compared with the molecular structure and concentrations used of proven plasticizers, solvents or additives for plastics systems. On the criteria of the similarities, a small group of candidate resins is identified. Simple mixing and heating of a substantial concentration of the drug with the resin, as between two plates under pressure, enables identification of the better combinations for compatibility of the introduced materials and enables observation of the efficacy of the system. In the case of topical anesthetic products, efficacy is readily observed based on the onset time for numbness, and the degree of numbness achieved. In other cases, migration of the drug from the novel reservoir through cadaver tissue can be observed.

It was shown that the resin also is advantageously configured to deliver local or topical anesthetic in the exterior region of an incision or wound, e.g. the resin is configured to form a functional bandage or compress, or a transdermal patch for intact skin.

It was suggested that the device, as described, be combined with adhesive that promotes transport of the drug, i.e. the adhesive contains a drug, and the drug from the resin of the device is effective to replenish the drug in the adhesive. Specifically, it was mentioned that the drug in the adhesive and the drug dissolved or incorporated in the resin include topical anesthetics.

Topically anesthetizing plastic fibers, sutures and textile layers, functional bandages and compresses and methods of manufacture of such devices were discussed.

It was also suggested in WO 98/39042 that transdermal patches be employed to apply topical

anesthetic or drug to or through the skin, making use of high concentrations of lidocaine as a tackifier to form a tackified methyl methacrylate-based adhesive useful as a transfer layer or as a significant drug releasing reservoir, and that use be made of plastisols for fabricating products including sheets, foams, films and coatings and formulation of adhesives that employ solid plastic particles of e.g. PVC, in which a drug such as lidocaine is present. A drug delivery or anesthetic delivery foam ear plug, foam nasal plug, foam drug or anesthetic delivery rectal, vaginal or other suppository, a dental appliance, a sublingual or buccal insert, and anesthetizing hot water bottles, ice packs and cushions were disclosed.

In WO 97/04948 it was mentioned that a plastisol approach offers advantages. To achieve a low temperature plastisol a low concentration of a suitable alcohol is included to form a plastisol composition, for example the plastisol is formulated with lidocaine base, polyvinyl chloride and an alcohol such as lauryl or oleyl alcohol.

Also for a low temperature plastisol, it was shown that a composition can include prilocaine in combination with lidocaine and PVC. Lidocaine base (a crystalline white substance at room temperature) is very soluble in prilocaine base (an oily liquid). A 50%-50% oily liquid eutectic mixture forms a pourable plastisol when mixed in equal amounts with solution grade PVC, with no other ingredients. Prilocaine has the potential disadvantage of producing methemoglobinemia in large systemic dosage.

One plastisol illustrated was made of a mixture of 25% prilocaine, 25% lidocaine and 50% polyvinyl chloride, by weight. The combination is a thick liquid painted or

applied as coating and heat cured to form a very tough tenacious coating that is very easily handled. The resultant product has excellent topical anesthetizing properties for certain purposes.

As an example of use, a plastisol formed with the combination of lidocaine and one of the alcohols just mentioned, and PVC of solution grade, or with prilocaine as mentioned, was screen printed on cotton surgical gauze and then heated to about 275°-300° F briefly to form a spot form or other pattern of anesthetic coating. Lidocaine-PVC plastisols were also suggested to create pain relieving devices as when the plastisol is molded to form the device or is coated on a preformed device.

Summary of the Invention

The present invention provides a system that takes advantage of the earlier discoveries, and provides novel plastisol and adhesive techniques that lead to simple and effective systems that are easy to manufacture.

In particular, a transdermal patch is achieved, which can have a number of desired attributes, i.e. simplicity of manufacture, good adherence and drug transfer to the skin, large concentration but low total drug present, and avoidance of transfer of adhesive to the skin.

Importantly, these goals are found to be achievable in a transparent transdermal patch, that, while cosmetically pleasing, enables effective drug delivery. Thus a cosmetically appealing patch or sheet can be worn on the face, legs or other part of the anatomy to produce topical anesthesia to prepare for minor surgical or laser procedures, hair removal, needle stick, i.v.s, etc., or otherwise to alleviate pain or discomfort.

In another case, a simple patch can administer drugs for various levels and types of pain relief, including safe dosages of narcotics or opiates, including fentanyl. The high drug concentrations possible, while present in very thin films, enable effective administration while avoiding the need to have present a large total quantity of the drug.

According to one aspect of the invention, a transdermal drug delivery system for delivering a drug component comprises, on a carrier, a layer comprising the combination of pressure sensitive adhesive having solids in which a drug component is substantially soluble, a non-adhesive polymeric resin distributed uniformly in non-particulate manner through the adhesive, and said drug component.

According to another aspect of the invention, a transdermal drug delivery system for delivering a drug component comprises a non-adhesive layer of polymeric resin in which a drug component is in substantial solution and an adjoining adhesive band arranged to hold the non-adhesive layer against the skin.

In the case of both of these drug delivery systems, the drug component preferably comprises at least 10% by weight of the drug-containing layer, preferably in excess of 20%, or 30% or 40% by weight. Indeed, it is discovered that concentrations in excess of 50% and even 60% can be achieved in effective formulations, which, importantly, can lead to faster initiation of drug effectiveness. Also, preferably the layer is sufficiently thin that there is no more than about 30 mg per inch square of drug present in the layer, preferably no more than about 20 mg or 10 mg per inch square.

In preferred embodiments of the invention the drug of the drug component incorporates at least one free amide or amine hydrogen in its structure, and preferably the drug of the drug component has the structure.

$$Bz - Z - (CH_2)_n - NR^1 R^2$$

where:

Bz is a substituted or unsubstituted benzene ring;
Z is an ester or amide linkage;
and each R^1 and R^2, individually, is Hydrogen or an alkyl group, or together form a 5 or a 6 member ring with the Nitrogen, and n is an integer.

In preferred embodiments, the polymeric resin and the drug are related as a congealed plasitsol.

Also, preferably the layer is transparent, and preferably the layer is disposed on a transparent support.

In important case the drug is selected to be active upon nerves or an aspect of the nervous system; or the drug is an anesthetic, topical anesthetic, analgesic, a narcotic or opiate, or a stimulant of the nervous system, e.g. a psychostimulant; or the drug has local anesthetic properties, or is an antiarrhythmic or antiseizure drug, an adrenergic blocking drug, a sympathomimetic drug, an analgesic or antipyretic drug or a drug that stimulates the nervous system.

In certain important cases, especially to achieve a high concentration of effective drug, the drug component comprises at least two drugs, one of which is soluble in the other, a solution of the drugs in the quantities present in the layer having a melting temperature below room temperature, and lower than the melting temperature of either drug alone.

In preferred examples of this aspect one of the drugs is an ester and one of the drugs is an amide; or one of the drugs is tetracaine and one of the drugs is lidocaine.

In the case of the drug delivery system having an adhesive, preferably the adhesive is an acrylic adhesive or methacrylate resin.

In certain preferred embodiments of each aspect of the invention, the polymeric resin is PVC or, more generally, the polymeric resin is selected from the group comprising polymers and copolymers of polyvinylchloride, other polymerized vinyl halides, chlorinated polyethylene, other halogenated polyolefins, ethylene propylene, cellulose resins such as cellulose nitrate, ethyl cellulose, and cellulose acetate, polystyrene, polyvinyl butyryl, acrylic resins, alkyl alkylacrylates, alkyl acrylates, acrylonitrile rubbers and chlorinated rubbers, polyesters, polyamides and polyformaldehyde.

In certain preferred embodiments of the drug delivery system the drug is selected from the group consisting of procaine, mepivacaine, bupivicane, lidocaine, chloroprocaine, cocaine, tetracaine, etidoncaine, prilocaine, etidocaine, replivicaine, diphenhydramine, and benzocaine.

In another preferred embodiment, the drug is fentanyl.

A specific aspect of the invention is a pressure sensitive adhesive drug delivery component comprising medical grade pressure sensitive acrylic adhesive, tetracaine, lidocaine and polyvinyl chloride, preferred embodiments having the proportions given in the examples.

In preferred cases, the component is combined with polyvinylchorlide and distributed in the adhesive uniformly in a non-particulate manner.

Another specific aspect of the invention is a plastisol or a congealed plastisol layer comprising tetracaine, lidocaine and polyvinyl chloride, preferred embodiments having the proportions given in the examples.

In preferred cases, the component or plastisol is combined with a volatile alcohol, as a paintable, coatable or sprayable composition, preferably using isopropyl alcohol.

In preferred cases the component, plastisol, composition, or congealed plastisol has weight ratio of combined lidocaine and tetracaine to the combined adhesive solids and polyvinylchloride or the polychloride when it appears alone greater than 50% or 60%.

In preferred embodiments the system in combination with a cushion arranged to press the drug containing layer against the skin, preferably the cushion being a foam layer of the drug-containing layer in a foam form.

Also according to the invention, a method of forming a drug-containing pressure sensitive adhesive layer or non- adhesive layer is provided, comprising combining the ingredients of the aforementioned first and second aspects of the invention, respectively, applying the resultant fluid to a substrate, and heating the substrate, preferably the proportions being as disclosed in the examples.

Preferred embodiments of the method have one or more of the following features.

A Volatile solvent is added to the resultant fluid to condition the fluid prior to applying the fluid to the substrate, preferably the solvent being an alcohol.

The fluid is applied to the substrate by roll coating, knife coating, spraying or printing.

Also a method of preparation of a drug delivery system is provided comprising preparing a plastisol containing polymeric resin or an adhesive solution containing polymeric adhesive solids and a drug component soluble by at least 25% by weight in the polymeric resin or adhesive solids and roll coating, knife coating, or spraying the plastisol or adhesive solution, suitably diluted upon a substrate.

Also, a preparatory swab for a transdermal drug delivery system is provided comprising a combination of lauramid DEA and epenipherine or a hydroxide buffer.

Drawings

Figures 1-1d illustrate various stages in the manufacture of a transdermal patch, while Figures 1e and 1f illustrate alternative constructions;

Figure 2 illustrates the presentation of a series of patches on a continuous sheet of release liner while Fig. 3 illustrates an elongated layer of drug-containing plastic presented in roll form.

Figures 4, 5, and 6 are diagrams illustrating alternative techniques for applying a plastisol coating to a substrate, for use in forming such products as are shown in Figures 1-3.

The drawings and descriptions of the above-referenced published patents and patent applications are also incorporated by reference.

Description of Preferred Embodiments

Referring to Figs. 1-1d, the formation of a transdermal patch is illustrated.

A flexible backing layer 10, of, for instance, polyvinyl chloride, polyethylene or polyester, is coated with a compatible pressure sensitive adhesive, medical grade, of type commonly employed to secure adhesive bandages or tape to the skin. From this sheet a disc is die cut, of form shown. A plastic sheet containing the desired drug is prepared in accordance with techniques described.

In preferred embodiments, a PVC plastisol layer 12 that contains the drug is applied to a carrier sheet 16 of polyester or polyethylene, followed by heating to congeal the plastisol. As shown, a circular disc coated with the drug-containing plastic is formed by cutting, of diameter somewhat smaller than that of the carrier disc 10. The drug-carrying disc is deposited centrally on the adhesive layer 12 of the backing disc, so that an annular rim of adhesive is exposed, and the drug-containing plastic layer 14 faces outwardly.

A pair of release sheets 22, 24, Fig 1b, e.g. of silicone coated paper, or plastic, are applied to form the assemblage of Figs. 1c and d. By grasping the upstanding tabs 26, the release sheet is removed, to prepare the patch for application to the skin.

The patch of Fig 1e is constructed in similar fashion to that of Fig 1d, with the addition of a resilient foam cushion 30 disposed between the adhesive carrier sheet and the drug-containing plastic assembly. When the surrounding rim of adhesive is applied to the skin, the cushion 10 serves to ensure intimate contact of the drug-containing plastic with the skin. This arrangement may be used to advantage in cases of large patches.

The transdermal patch of Fig. 1f is also similar to that of Fig. 1c, except that the drug-containing plastic plastisol is deposited directly on carrier sheet 10, to serve as a reservoir of the drug, and a compatible pressure sensitive adhesive (cross linked acrylic adhesive), such as Monsanto 1753 is applied over the surface of the cured plastisol. The adhesive may have the drug preloaded into it, for accelerating the onset, or natural diffusion may be employed to achieve equilibrium conditions by migration of the drug into the adhesive after deposit.

The patches of Figs. 1 and 1f are typically transparent and cosmetically attractive. The patch of Fig 1e. may likewise be cosmetically attractive by choice of a clear resin cushion that is suitably thin.

In cases where the drugs are topical anesthetics, the patches are suitable, for instance, to apply to the nose, face, arms, arm pits, legs and abdomen overnight in anticipation of laser treatment for peels and removal of hair, scars, blemishes, vascular capillaries, for waxing or electrolysis hair removal, etc.

These patches are also useful to prepare areas of the skin for needle stick, especially for children and for areas that are repeatedly penetrated by needles and have developed sensitivity. Examples are the accessing of subcutaneous vascular ports and the injection of botulism toxins to treat blephero spasms (spasms of the eyelid) or dynamic rhytidics (uncontrollable blinking).

As shown in Fig 2, in another form, the patches according to Fig 1a are applied face down upon a continuous release sheet, which is supplied to the consumer, e.g. in the form of a roll.

In the example of Fig. 3, a central band of plastisol 14 is applied and cured on a carrier sheet 10 of wider width, and adhesive 12 is applied along each side. The carrier sheet 10 and adhesive are compatibly selected to permit release, so that the assemblage is wound into a roll for dispensing, without need for an intervening release layer.

For applying the plastisol to a carrier sheet in production, various techniques can be employed. Fig. 4 illustrates roll coating application of the plastisol 14 to the carrier sheet 16; Fig 5 illustrates knife coating of the plastisol upon carrier sheet 16; and Fig. 6 illustrates spray application according to the techniques described below.

Example I

At room temperature, into a mortar were placed, by weight, 1 part tetracaine base and 1 part lidocaine base, in crystalline powder form. The powders were heated by a heat gun to approximately 150° F to form a clear liquid solution of tetracaine lidocaine which remained liquid and clear when cooled to 45° F. The solution was mixed with 1 part emulsion grade polyvinyl chloride by pestle to produce a smooth and nearly clear viscous fluid. Ethyl alcohol was added, reducing the fluid's viscosity to a consistency capable of being painted as a thin layer. It had a milky white appearance. The plastisol mixture was painted uniformly as a thin film upon a clear polyester film substrate of 10 inch by 14 inch dimension secured to an aluminum carrier plate. The plate and coated sheet were placed in an oven at 225° F for 3 minutes and removed. This resulted in a thin, solid, flexible, non-tacky, drug-containing coating which adhered to the polyester film, comprised of $33^{1}/_{3}$% each of

tetracaine, lidocaine and PVC, by weight, total drug 66 $^{2}/_{3}$%. The overall product was transparent.

After aging for two weeks, one half inch diameter discs were cut from the product, following which the polyester sides of the discs were placed upon the adhesive side of discs of three quarter inch diameter and five eights inch diameter cut from medical grade clear adhesive tape. The resultant transparent patches had a solid non-tacky active center area of cured plastisol surrounded by an annulus of pressure sensitive adhesive. The active area of a patch contained about 1 mg tetracaine and 1 mg lidocaine. A protective release layer was applied over each assemblage, held in place by the rim of the adhesive.

Skin of a subject was prepared, in one case, by washing with warm soapy water, and, without rinsing, dried. In another case, previously washed and rinsed skin was prepared by washing with plain warm water and dried. The release layers were removed and the patches were applied to the prepared skin.

Both sizes of patches were firmly retained on the skin. A profound topical block was produced in about 45 minutes in both cases, as determined by employing No. 23 needle penetration.

Example II

At room temperature, into a mortar were placed, by weight, 3 parts tetracaine base and 2 parts lidocaine base, crystalline powders. The powders were heated by a heat gun to approximately 150° F to form a clear liquid solution of the drugs. The solution while still warm was mixed by pestle with 1 part emulsion grade polyvinyl chloride to produce a smooth and nearly clear viscous fluid.

Into this fluid were mixed 6 parts Monsanto Medical grade adhesive solution No. 1753 (comprising 2 parts acrylic solids and 4 parts volatile solvents). This formed a more viscous, semi-clear fluid. Ethyl alcohol was added to reduce the fluid's viscosity to a paintable consistency, having a milky white appearance.

The mixture was painted as a thin uniform coating upon a thin, clear polyester film substrate of 10 inch x 14 inch dimension mounted on an aluminum carrier plate. The plate and coated sheet were placed in an oven at 225° F for three minutes. This produced a thin, transparent, drug-containing film which strongly adhered to the polyester substrate, having desirable pressure-sensitive characteristics. The film contained, per square inch coating, 5 mg tetracaine base, and 3.25 mg lidocaine base, in the presence of 3.25 mg medical grade adhesive solids of 1.65 mg polyvinyl chloride. (The coating thus contained 37.5% tetracaine, 25% lidocaine, 12.5% polyvinyl chloride and 25% acrylic adhesive solids, by weight, total drug 62.5%, and appears as a uniform single phase solid solution, without particulates.)

A silicon-coated release sheet was applied to the adhesive, and patches of varying size were cut from the assemblage, including rectangular sheets or patches 2 inch x 4 inch dimension.

These patches were placed upon skin prepared with, in one case, betadine scrub, and in other cases, warm soapy water and plain water as in the previous example.

In each case noticeable topical anesthetic block was observed by No. 23 needle penetration in about 1 hour and substantially total block observed in ninety minutes, somewhat faster action being indicated with skin washed with betadine scrub or soapy water and dried without rinsing. A slight trace of residual adhesive was observed on the skin prepared with plain water, while

none was observed with skin prepared with soapy water and dried without rinsing.

The non-transfer of adhesive to the skin during removal compared very favorably with similar products in which the PVC was omitted from the mixture.

Example III

The procedure of Example 2 was followed with the proportions of ingredients altered to produce a coating of 32% tetracaine, 18% lidocaine, 32% acrylic adhesive solids and 18% polyvinyl chloride. Anesthetic performance substantially the same as Example 2 was observed, with no transfer of adhesive to skin prepared with plain or soapy water, the improved performance over Example II in respect of non-transfer of the adhesive to the skin being attributed to the increased percentage of PVC in the solution.

Example IV

Coated sheets were prepared according to Examples I, II, and III. Upon the adhesive side of sheets from examples II and III were placed discs and other shapes cut from the sheet of Example I. The underlying sheets were cut leaving a perimeter band of adhesive about the discs and other shapes. The resulting transdermal patches had areas of solid, fast-acting drug-containing plastisol, surrounded by securing bands of drug-containing pressure-sensitive adhesive, so that the entire patch including its perimeter adhesive rim was active in drug delivery.

Further Plastisol Examples V

The range of concentrations of anesthetic that can be employed using plastisol techniques, and of conditions

of manufacture and use are illustrated in the following examples.

For these examples a plastisol was prepared by mixing powdered polyvinyl chloride (emulsion grade), with a fluid comprising either (a) a single anesthetic base in combination with isopropyl alcohol, (b) a non-alcohol mixture of two topical anesthetic bases, the mixture having a lower melting temperature than either of the anesthetics alone, (c) a water suspension of an anesthetic base or (d) a solution of anesthetic base and lauryl alcohol. All transdermal patch examples were applied to the arm of a white adult male.

The first set of examples 1-5, employed a single topical anesthetic, lidocaine base, combined with polyvinyl chloride and isopropyl alcohol.

Example 1:

60 grams lidocaine base and 120 grams PVC powder were combined by mixing in a household blender with 300 cc's by volume isopropyl alcohol. A paintable fluid plastisol was formed (with lowered concentrations of alcohol, mixtures became thicker and less paintable). The fluid was painted upon a plastisol film carrier sheet of PET (polyethylene terephthalate, i.e. du Pont's Mylar) such as is employed in turkey baking bags, with the sheet taped flat to a thin metal carrier plate. The painted sheet was heated to 225°F for a period of 2 minutes, driving off the alcohol and congealing the powdered resin anesthetic combination. The result was a clear, solid, flexible anesthetic plastic layer on the carrier. The composite was wrinkle free and appeared more pliable than a PET sheet by itself due to a "rubberizing" effect of the anesthetic layer, non-tacky layer that contained 33% lidocaine base. When the anesthetic plastic layer was placed in contact directly with the skin, a superficial

anesthetic block was achieved with a 3 hour onset. The block had 15-20 minute persistence after removal. The block attained was sufficient for the subject to withstand a pin prick of the skin without pain. This relatively low concentration of anesthetic is suitable for prolonged use over large areas of skin subject to chronic discomfort, such as burn dressings and treatment of post-hepatic neuralgia and other hypersensitivity skin states such as causalgia.

Thickness of the anesthetic plastic layer, hence drug availability over time per unit area, is varied depending upon duration of the effect desired.

A coating containing approximately Lidocaine 25 mg/ 1 in^2 is found to produce a numbing block of the skin for 24-36 hours.

Example 2:

The procedure of Example 1 was followed employing 80 grams lidocaine base, 120 grams PVC, providing a 40%-60% ratio of anesthetic to PVC, mixed with 60 cc's isopropyl alcohol. This formed a very thin paintable plastisol, the less alcohol required being attributable to the higher concentration of the anesthetic base. The plastisol was painted upon a PET carrier sheet according to example 1 and baked at 225°F for 2 minutes. It formed a solid, flexible, slightly tacky anesthetic plastic layer upon the substrate having contact clarity (slightly translucent). A trace concentration of microscopic precipitated anesthetic crystals was observed. When the coating was held in skin contact it provided a somewhat moderate anesthetic block after 2 $^1/_2$+ hour onset, of 15-20 minutes duration following removal of the patch. The block was sufficient for the subject to withstand pin prick of the skin without pain. The resultant product is

suitable for application to moderately large areas of the skin for treatment, e.g. of chronic discomfort.

Example 3:

The procedure of Example 1 was followed, using a 50-50 lidocaine-PVC mixture; 100 grams of lidocaine base and 100 grams PVC were mixed with 60 cc's of isopropyl alcohol to form a thin fluid paintable plastisol. The plastisol was painted on PET film and baked at 225° F for 2 minutes. It formed a translucent, solid, flexible, slightly tacky anesthetic plastic layer upon the carrier, containing 50% anesthetic base. Microscopic precipitated anesthetic crystals were more pronounced than in Example 2. The layer produced a moderate block following a 2 1/2 hour onset, with approximately 15 to 20 minutes duration following removal from the skin. The block was sufficient for the subject to withstand pin prick without pain, and after presence for 12 hours, penetration by No. 23 needle without pain occurred. The block is sufficient to facilitate minor dermatological procedures, such as laser treatments for the removal of hair or cosmetic imperfections.

Example 4:

The same conditions as Example 3 were employed, but using a polyethylene sheet of .0007 inch thickness (food storage bag material). The resulting composite product was more compliant, exhibiting less tensile strength than Example 3, and greater conformability.

Example 5:

The procedure of Example 1 was employed with a 60 to 40 ratio of lidocaine base to PVC. 120 grams of lidocaine base and 80 grams of PVC were mixed with 60 cc's isopropyl alcohol to form a very thin, fluid

plastisol. When applied by paintbrush to PET film upon a metal base sheet and baked at 225° F for 2 minutes, it formed a translucent, solid, flexible, barely tacky anesthetic plastic layer with a high concentration of precipitated anesthetic crystals. It demonstrated 2 $^{1}/_{4}$ hour onset of a moderate block, with 15 to 25 minutes duration following removal. The block was sufficient to withstand penetration with a 23 needle without pain.

Examples 6 and 7, now to be described, employed a mixture of tetracaine and lidocaine that formed an oily liquid at room temperature, a so called "eutectic". No other fluid component was employed.

Example 6:

A 60% anesthetic, 40% PVC mixture was prepared, the anesthetic comprising equal parts by weight of tetracaine base and lidocaine base so that the ratios of the total were 30% tetracaine, 30% lidocaine and 40% PVC. The three ingredients formed a thick fluid plastisol capable of being applied with a squeegee. The plastisol was applied to a carrier film of PET and baked at 250° F for 2 minutes. It formed a clear, solid, flexible anesthetic plastic layer having a tacky surface with microscopic eutectic fluid at the surface. It produced a profound block with 1 $^{1}/_{2}$ hour onset. Penetration with a No. 23 needle occurred without pain. Duration of the block after removal of the transdermal patch was one hour. Slight reddening of the skin that occurred was useful to mark the anesthetized area for the procedure following.

The depth of block and duration were sufficient to facilitate dermatological procedures, such as needle aspiration biopsy, laser removal of skin lesions and hair removal, as by laser, waxing or electrolysis.

Example 7:

The procedure of Example 6 was followed, except that the carrier sheet was polyethylene film and the mixture was 50% anesthetic to 50% PVC, employing 33% tetracaine base and 17% lidocaine base, by weight in a "eutectic" mixture. This formed a thick fluid plastisol and was applied with a squeegee to the polyethylene film and baked at 250° F for 2 minutes. It formed a slightly translucent (contact clarity) solid flexible anesthetic plastic layer that was slightly tacky, with some precipitated anesthetic crystals. It demonstrated a profound block within 1 $^{1}/_{2}$ hour, suitable to withstand penetration by a No. 23 needle without pain. The block lasted for one hour following removal of the patch, with some reddening of the skin observed.

Example 8:

To a dry mixture of 50% lidocaine base, 50% PVC, was added water in a household blender and 30cc of Betadine Scrub (a commercial surgical antiseptic cleansing solution containing povidone-iodyne and lauramide DEA, available from The Purdue Frederick Company, Norwalk, CT).

Sufficient water was introduced to produce a frothy, paintable suspension. The suspension was painted upon a PET sheet and baked at 250° for five minutes.

A congealed, slightly tacky coating was produced which was translucent but demonstrated substantial contact clarity when pressed upon the skin, the coating having a slight yellowish hue attributable to the Betadine. The results were similar to Example 3.

The examples so far described that employ isopropyl alcohol or water to form a plastisol depended upon volatilization of the alcohol or water during

preparation and in the baking such that none remained and the PVC congealed to form a continuous coating. When using this system to form a thick layer or object, a degree of porosity of the product can be obtained, which in certain circumstances can be advantageous. Blowing agents can also be employed when porosity or foam is desired.

In the case of employing anesthetic mixtures that are liquid at room temperature, no volatilization occurs and the plastisols can be produced in thick layers or molded forms without porosity.

Other examples of useful plastisols employ suspending fluids that do not volatilize during baking and permit forming articles with significant thickness without porosity. Examples of such fluids are oleyl and lauryl alcohols. Lauryl alcohol is found to be highly compatible with PVC and is employed in the following examples.

Example 9:

A plastisol comprised of 20% lauryl alcohol, 40% lidocaine base, and 40% PVC, by weight, were mixed to form a paintable fluid. The plastisol was painted upon a PET carrier sheet and baked as in Example 1. Results similar to those of Example 2 were obtained. Multiple anesthetic plastic layers can also be formed with heating between applications.

Example 10:

The Example 9 was repeated employing 16% lauryl alcohol, 42% lidocaine base and 42% pvc.

The results are given in the following table:

Example	L	T	PVC	% Anesthetic	Added Fluid	Type of Elastisol	Clarity	Crystal Conc.	Time of Onset	Persistence Minutes	Block
1	60g		120g	30%	alcohol 300cc	thin	clear	none	3hr	15-20	pin prick
2	80g		120g	40%	alcohol 60cc	thin	transl	slight	2½hr	15-20	pin prick
3 and 4	100g		100g	50%	alcohol 60cc	thin	transl	mod.	2½hr	15-20	pin prick
5 5	120g		80g	60%	alcohol 60cc	thin	transl	high	2½hr	15-25	#23 needle
6	30%	30%	40%	60%	none	thick	clear	none	1½hr	60	#23 needle
7	17%	33%	50%	40%	none	thick	clear	slight	1½hr	60	#23 needle
8 and 9	40%		40%	40%	20% lauryl alcohol	paintable					
10	42%		42%	42%	16% lauryl alcohol	thick					

Example 11:

A brass tube mold form was covered with starch powder. Three coatings of the plastisol formed in Example 9 were applied to the mold form with heating of each coating before applying the next. Heating was by air from a hot air gun, estimated to have a temperature of 225° to 250° F. After the three successive coatings were applied and successively heated, the resulting tubular plastic article was removed from the brass tubular mold by rolling off. The result was a highly flexible, soft tube of approximately 1/2 inch diameter having a wall thickness of approximately .040 inch, suitable for use as a penrose drain. Anesthetization of tissue of the patient with such a tube in place can reduce or eliminate pain during recovery and during removal of the drain tube by typical pulling from the wound.

Example 12:

The moldability of a material in numerous forms was demonstrated. A plastisol of 16% lauryl alcohol, 42% lidocaine base and 42% PVC was mixed to form a moldable thick fluid. The fluid was poured upon a plate. A number of elements was placed upon the fluid: a safety razor blade, coins of a variety of shapes and surgical scissors. The assembly was placed in an oven and heated to 225° F for approximately 5 minutes. The resultant member was a flacid, congealed rubbery sheet, $^1/_8$ inch thick, approximately 8 inches by 5 inches in breadth, from which all of the objects were readily released. In the instance of the coins, extremely thin films were formed beneath the coins, the film material exactly replicating the negative shape of the face of the coins and their edge knurling. Likewise, detailed impressions of the safety razor and scissors were formed.

Similarly, as has been previously described, deposition or molding of foams and printing of plastisols on compresses, bandages and the like can be prepared.

Example 13:

Transdermal patches were formed with the material of Examples 1 through 9 and applied directly to the skin, held in place by a pressure sensitive adhesive border that surrounded the anesthetic patch. The border was provided by an overlying sheet that extended beyond the dimensions of a segment of the plastisol coated film. In other cases a separate pressure-sensitive adhesive tape was employed to secure an anesthetic segment against the skin.

Example 14:

Examples similar to Example 13 were prepared, with the adhesive also containing anesthetic, to avoid pain during removal from hairy skin, and the like.

To form such an assemblage, a film carrier sheet such as PET or polyethylene is coated with adhesive that contains the anesthetic. A segment of the material described in any of the examples 1 through 9 is then deposited upon the adhesive sheet, leaving margins of the adhesive sheet exposed, to which is then applied a release sheet.

In preparing an adhesive carrier sheet or adhesive tape it is preferred to employ a cross-linked acrylic adhesive, such as Monsanto 1753 adhesive, mixed with 15% by weight lidocaine base or 10% tetracaine base. The 1753 Monsanto adhesive contains a solvent that maintains the mixture in liquid form prior to application. The adhesive is painted on the carrier sheet, e.g. PET or polyethylene film and baked as previously described. This results in an

adhesive carrier sheet that is entirely clear; i.e., the anesthetic is in solution in the adhesive residue after evaporation of the solvent, and provides an anesthetizing pressure-sensitive adhesive sheet or tape. For forming transdermal patches, a pre-formed segment of the material of any of the examples 1 through 9 is applied to a central area of the adhesive carrier sheet or tape and, after application of release paper to the borders extending beyond the plastisol segment, an outline is cut or stamped to form the final patch, which is then appropriately packaged and sterilized.

Example 15:

In preparation for application of a patch, a sponge was prepared comprising 1cc of epinephrine (1:1000, in water) and 1cc of Betadine scrub. The sponge was packaged in a vapor barrier pouch. Prior to application of an anesthetic patch as previously described, the sponge was removed from the pouch and used to scrub the receiving area. The onset of the block was accelerated by this treatment, while any reddening propensity of the anesthetic was markedly reduced.

Example 16:

An example of use of the sponge of Example 15 and an anesthetic patch is in needle aspiration biopsy. For instance, for taking tissue from enlarged thyroid, 1 $^1/_2$ hrs prior to the procedure, the skin in the lower neck region, over the thyroid, was swabbed with the Betadine-epinephrine sponge and allowed to dry. Segments of anesthetic plastic sheet fabricated according to Example 6 were placed upon somewhat larger adhesive sheets according to Example 13, to form transdermal anesthetic patches. The patches were

approximately 1 in. square overall, with the anesthetic plastic segments approximately $^{3}/_{4}$ x $^{3}/_{4}$ in. Four of these patches were applied over the thyroid on one side of the neck. 1 $^{1}/_{2}$ hours later the skin in areas beneath the anesthetic plastic segments were totally blocked. Slight redness of the skin, an effect of the tetracaine, remained at the sites of the anesthetic segments, serving as markers for the attending physician and pathologist.

Needle aspiration biopsy was then performed, with No. 23 needle inserted in the areas of slight redness. The patient had no sensation of penetration of the skin with the No. 23 needle.

The degree of redness can be increased if desired, by reducing the concentration of epinephrine in the swab. In other cases, other markers are associated with the patch, such as ridges that leave an indentation in the skin marking the anesthetic area of the patch, transfer dyes, etc.

Example 17:

A sponge was prepared using a 50/50% mixture of Betadine Scrub and a magnesium hydroxide buffer (Phillips Milk of Magnesia, 80 mg/ml magnesium hydroxide in purified water). The Ph of the mixture was 9.8. The forearm was wiped with the sponge and a segment of the sheet as prepared in Example 6 was applied. The preparation was found to increase the speed of onset and the depth of block. The effect is attributed to the store of residual magnesium hydroxide particles that maintained the alkaline condition during residence of the patch. A moderate block (insensitive to pin prick) was obtained within 1 hour, and by 1 $^{1}/_{2}$ hours a profound block was obtained, enabling penetration by a No. 23 needle, without sensation. Slight redness was observed. The block lasted for about 1 hour.

Example 18:

The procedure of Example 17 was repeated with the presence of epinephrine in the Betadine Scrub as described in Example 14. The same rapidity of onset and depth of block was obtained. No redness was observed.

Example 19:

A plastisol was prepared according to Example 8 (40% lidocaine, 40% PVC, 20% lauryl alcohol) and placed in a receptacle associated with a pressurized aerosol spray. The plastisol was sprayed upon a 4 inch wide strip of PET film using constant relative motion between the film and sprayer. The resulting deposit had a density of 20 mg/in^2.

After baking for 2 minutes at 220° F, a clear smooth coating of the anesthetic plastic was obtained.

Testing produced the results reported for Example 8.

The test was repeated with the same result.

This verifies the reliability of a production technique of advancing, for example, a 4" wide PET film substrate past a fixed aerosol sprayer, and advancing the coated substrate through an oven.

Delivery of Other Drugs

The specific examples involving the base form of topical anesthetic drugs of amide or ester type in PVC, and other carriers, has been presented by way of example. Many other drugs with a benzene ring are relatively highly soluble or can be incorporated in PVC and other hydrophobic plastics as has been discussed above, and can be incorporated in the novel patches and systems described. Similarly to the base form of local anesthetics, these drugs are slowly released to the surface of the polymer. Thus an

improved general mechanism for formulating time-released medications has been provided.

Rugged transdermal skin patches according to the invention provide high concentrations of selected drugs but still low total amount of drug in solid solution in durable polymers. Good adhesion is achieved without transfer of the adhesive to the skin when the patch is removed.

In transdermal systems according to the techniques disclosed there is no need to be concerned about the protection of liquids or delicate gels. Benefits include simpler packaging and storage, avoidance of need for precautions in user handling, protective incorporation in solid resin, low total weight of drug for a desired effect, and lowered cost.

What is claimed is:

1. A transdermal drug delivery system for delivering a drug component comprising, on a carrier, a layer comprising the combination of pressure sensitive adhesive having solids in which a drug component is substantially soluble, a non-adhesive polymeric resin distributed uniformly in non-particulate manner through the adhesive, and said drug component.

2. A transdermal drug delivery system for delivering a drug component comprising a non-adhesive layer of polymeric resin in which a drug component is in substantial solution and an adjoining adhesive band arranged to hold the non-adhesive layer against the skin.

3. The drug delivery system of claim 1 or 2 in which the drug component comprises at least 10% by weight of the drug-containing layer, preferably in excess of 20%, or 30% or 40% or 50% or 60% by weight.

4. The drug delivery system of claim 3 in which the layer is sufficiently thin that there is no more than about 30 mg per inch square of drug present in the layer, preferably no more than about 20 mg or 10 mg per inch square.

5. The drug delivery system of any of the foregoing claims in which a drug of the drug component incorporates at least one free amide or amine hydrogen in its structure.

6. The drug delivery system of any of the foregoing claims wherein a drug of the drug component has the structure

$Bz - Z - (CH_2)_n - NR^1 R^2$

where:

Bz is a substituted or unsubstituted benzene ring;

Z is an ester or amide linkage;

and each R^1 and R^2, individually, is Hydrogen or an alkyl group, or together form a 5 or a 6 member ring with the Nitrogen, and n is an integer.

7. The drug delivery system of any of the foregoing claims in which the polymeric resin and the drug are related as a congealed plasitsol.

8. The drug delivery system of any of the foregoing claims in which the layer is transparent.

9. The drug delivery system of claim 8 in which the layer is disposed on a transparent support.

10. The drug delivery system of any of the foregoing claims in which the drug is active upon nerves or an aspect of the nervous system.

11. The drug delivery system of any of the foregoing claims in which the drug is an anesthetic, topical anesthetic, analgesic, a narcotic or opiate, or a stimulant of the nervous system, e.g. a psychostimulant.

12. The drug delivery system of any of the foregoing claims 1-10 in the drug has local anesthetic properties, or is an antiarrhythmic or antiseizure drug, an adrenergic blocking drug, a sympathomimetic drug, an analgesic or antipyretic drug or a drug that stimulates the nervous system.

13. The drug delivery system of any of the foregoing claims in which the drug component comprises at least two drugs, one of which is soluble in the other, a solution of the drugs in the quantities present in the layer having a melting temperature below room temperature, and lower than the melting temperature of either drug alone.

14. The drug delivery system of claim 13 in which one of the drugs is an ester and one of the drugs is an amide.

15. The drug delivery system of claim 13 in which one of the drugs is tetracaine and one of the drugs is lidocaine.

16. The drug delivery system of claim 1 in which the adhesive is an acrylic adhesive of methacrylate resin.

17. The drug delivery system of any of the foregoing claims in which in which the polymeric resin is PVC.

18. The drug delivery system of any of the foregoing claims 1-16 in which the polymeric resin is selected from the group comprising polymers and copolymers of polyvinylchloride, other polymerized vinyl halides, chlorinated polyethylene, other halogenated polyolefins, ethylene propylene, cellulose resins such as cellulose nitrate, ethyl cellulose, and cellulose acetate, polystyrene, polyvinyl butyryl, acrylic resins, alkyl alkylacrylates, alkyl acrylates, acrylonitrile rubbers and chlorinated rubbers, polyesters, polyamides and polyformaldehyde.

19. The drug delivery system of any of the foregoing claims in which the drug is selected from the group consisting of procaine, mepivacaine, bupivicane, lidocaine, chloroprocaine, cocaine, tetracaine, etidoncaine, prilocaine, etidocaine, replivicaine, diphenhydramine, and benzocaine.

20. The drug delivery system of any of the foregoing claims 1-19 in which the drug is fentanyl.

21. A pressure sensitive adhesive drug delivery component comprising medical grade pressure sensitive acrylic adhesive, tetracaine, lidocaine and polyvinyl chloride.

22. The drug delivery component of claim 21 in which the polyvinylchorlide is distributed in the adhesive uniformly in a non-particulate manner.

23. A plastisol comprising tetracaine, lidocaine and polyvinyl chloride.

24. The component of claim 21 or 22 or plastisol of claim 23 in combination with a volatile alcohol as a paintable, coatable or sprayable composition, preferably isopropyl alcohol.

25. A congealed plastisol layer comprising tetracaine, lidocaine and polyvinylchloride.

26. The component of claim 21 or 22, the plastisol of claim 23, the composition of claim 24, or the congealed plastisol of claim 25 in which the weight ratio of combined lidocaine and tetracaine to the combined adhesive solids and polyvinylchloride or the polychloride when it appears alone is greater than 50% or 60%.

27. The drug deliver system of claim 2 or any claim as dependent thereon in combination with a cushion arranged to press the drug containing layer against the skin, preferably the cushion being a foam layer of the drug-containing layer in a foam form.

28. The method of forming a drug-containing pressure sensitive adhesive layer or non-adhesive layer, comprising combining the ingredients of claim 1 or 2, respectively, applying the resultant fluid to a substrate, and heating the substrate.

29. The method of claim 28 including adding a volatile solvent to the resultant fluid to condition the fluid prior to applying the fluid to the substrate, preferably the solvent being an alcohol.

30. The method of claim 28 or 29 in which the fluid is applied to the substrate by roll coating, knife coating, spraying or printing.

31. A method of preparation of a drug delivery system comprising preparing a plastisol containing polymeric resin or an adhesive solution containing polymeric adhesive solids and a drug component soluble by at least 25% by weight in the polymeric resin or adhesive solids and roll coating, knife coating, or spraying the plastisol or adhesive solution, suitably diluted upon a substrate.

32. A preparatory swab for a transdermal drug delivery system comprising a combination of lauramid DEA and epenipherine or a hydroxide buffer.

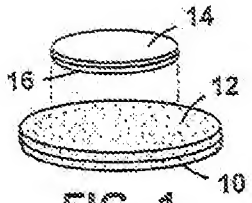

FIG. 1

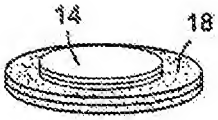

FIG. 1A

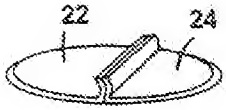

FIG. 1B

FIG. 1C

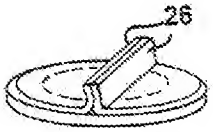

FIG. 1D

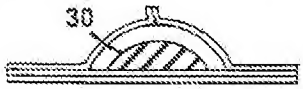

FIG. 1E

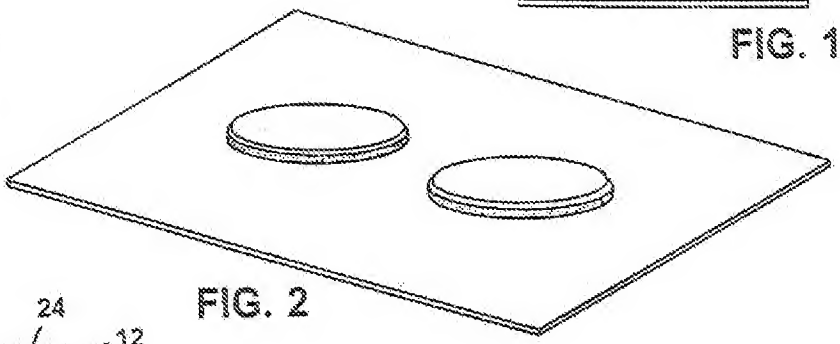

FIG. 2

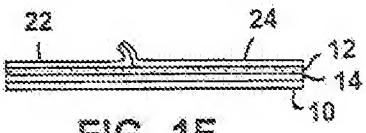

FIG. 1F

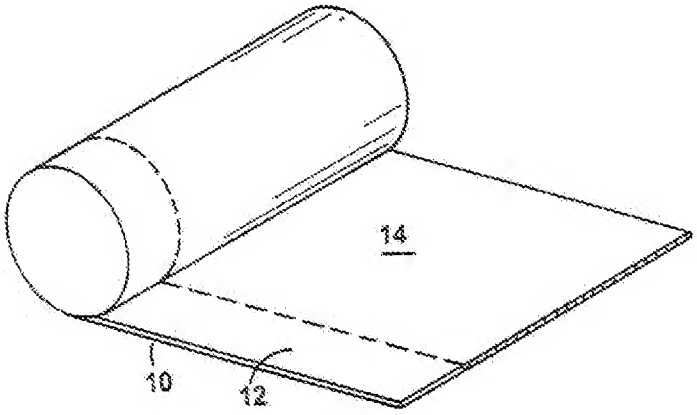

FIG. 3

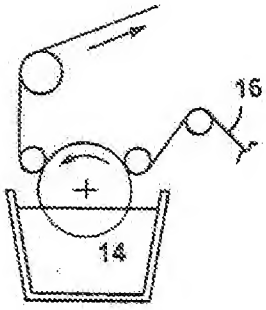

FIG. 4

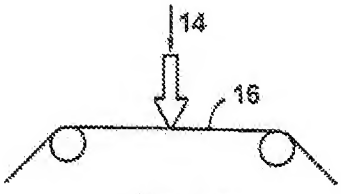

FIG. 5

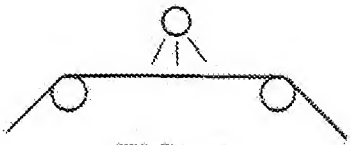

FIG. 6